

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



The role of microRNAs in gestational diabetes



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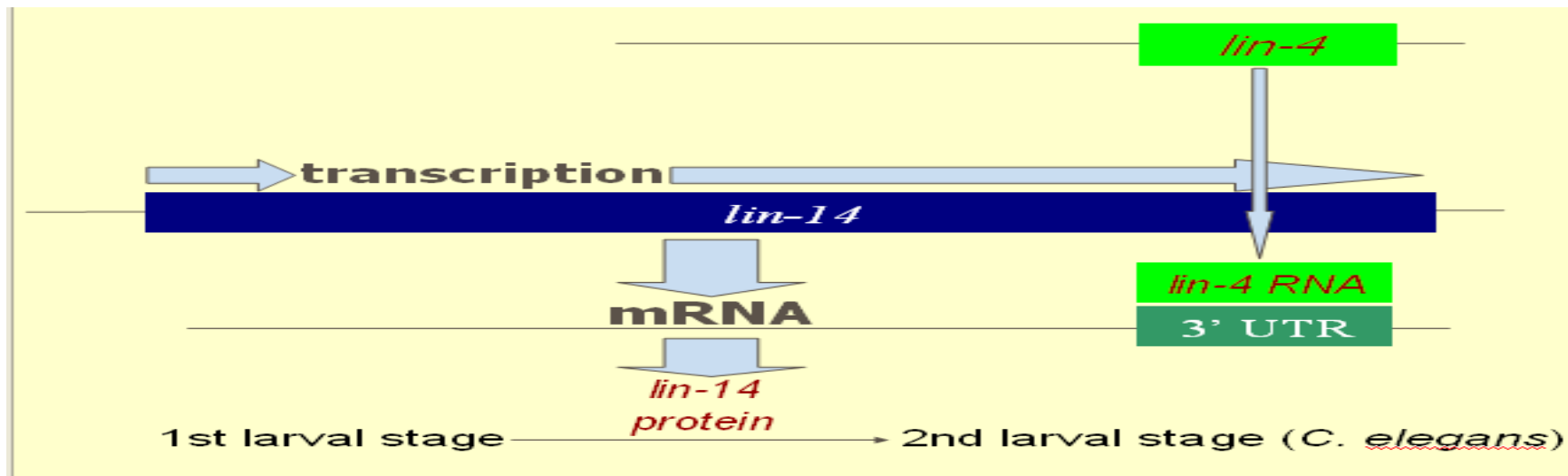
Exosomes and GDM

What is microRNA?

- ✓ Small non-coding double stranded RNAs
- ✓ Approximately 19-22 nt long
- ✓ Repress activity of complementary mRNAs
- ✓ Regulate 30% of mammalian gene products
- ✓ 1 miRNA = hundreds of mRNAs
- ✓ Have been described in invertebrates and vertebrates:
worms, fungi, plants, and mammals

History of microRNA

- 1993, Discover *lin-4*, the first miRNA in worm, Victor Ambrose et al.

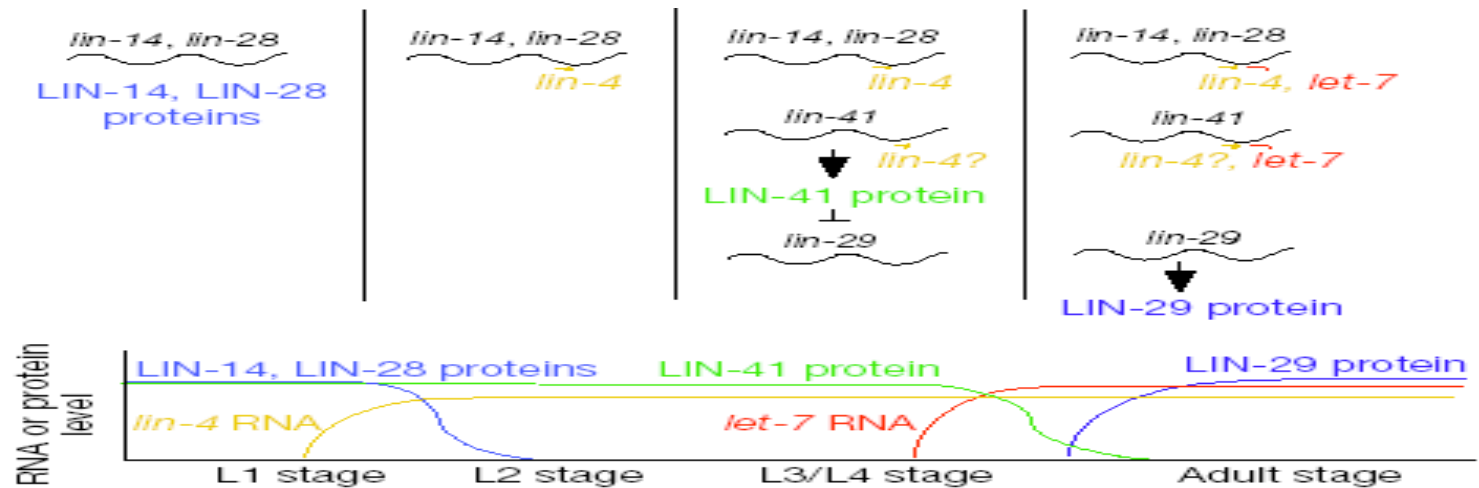


Cell 1993, Vol75;843-54

Presented by: Ghadimi
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History of microRNA

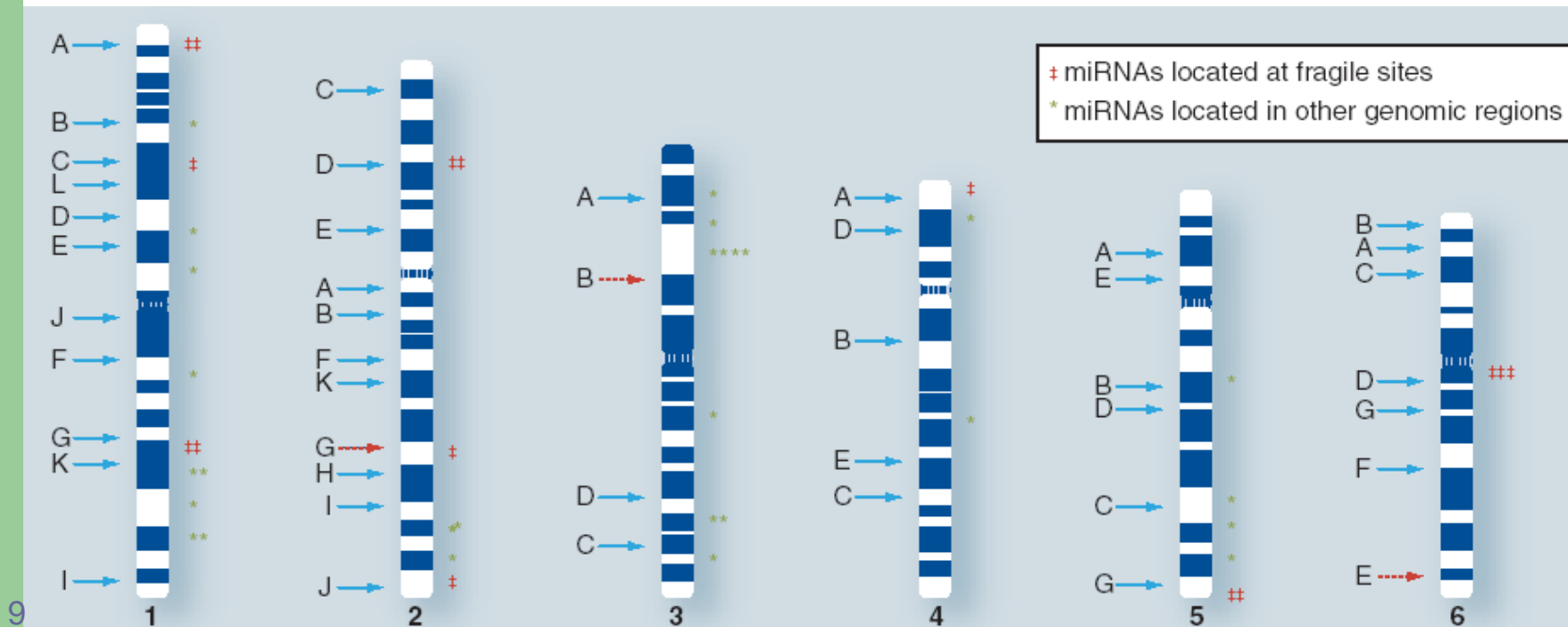
- 2000, discover the first evolutionarily conserved miRNA (*let-7*) in worm

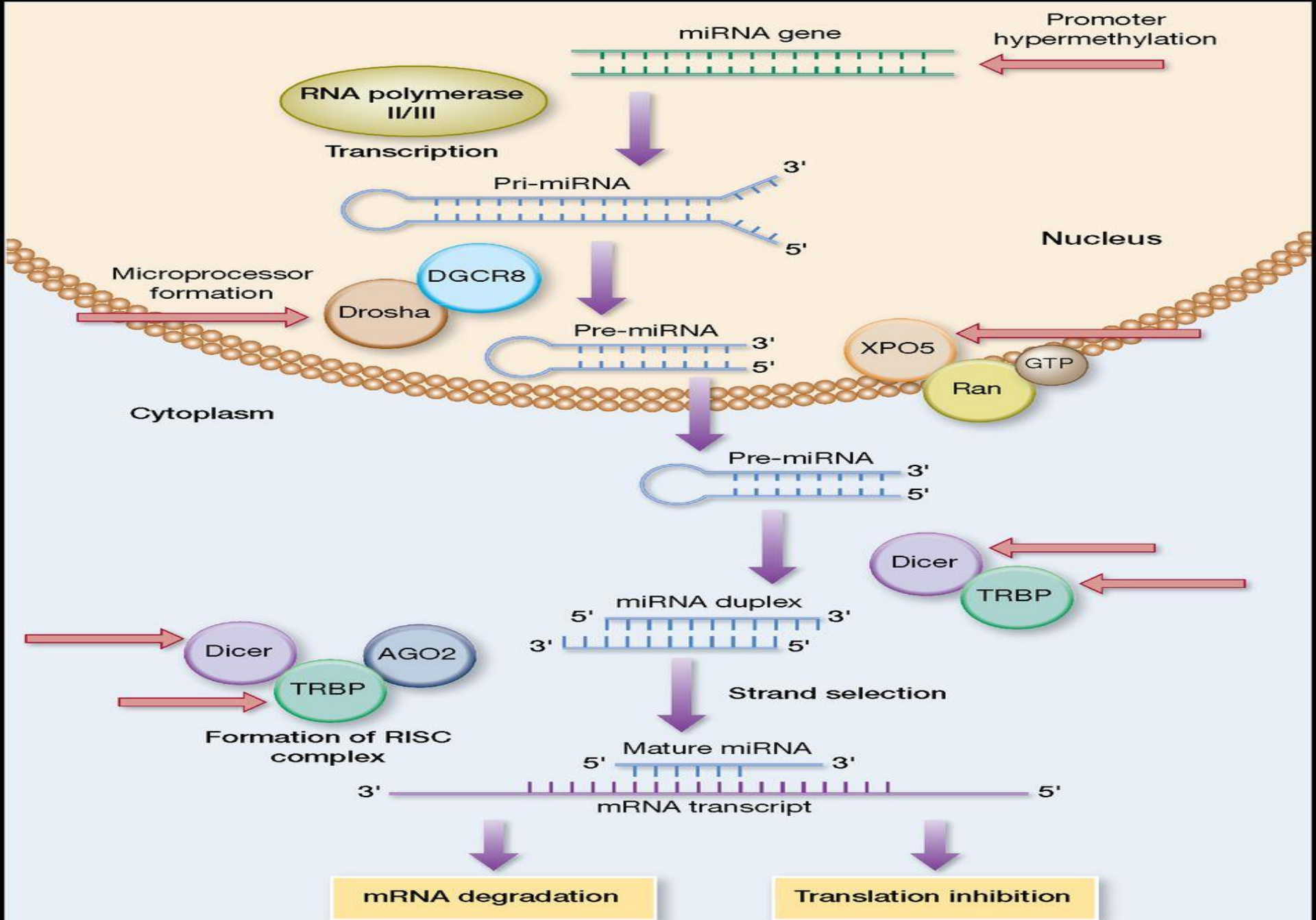


Nature 2000, Vol.403;901-5

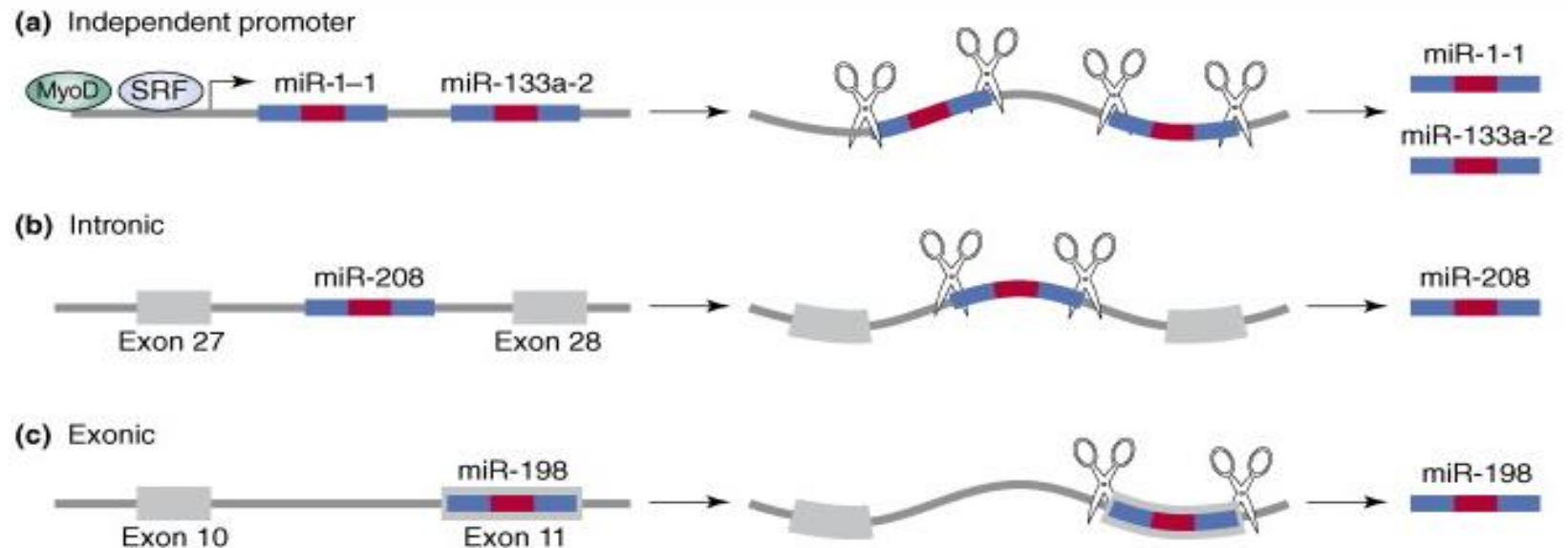
History of microRNA

- 2005, hundreds of miRNA gene discovered in human





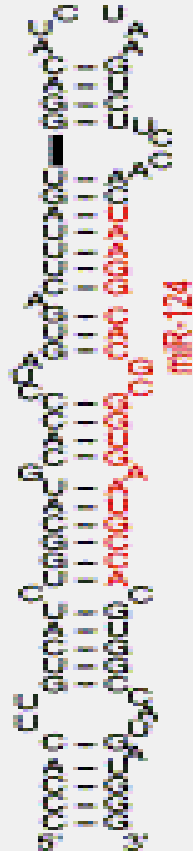
Genomic Organization of miRNA Genes



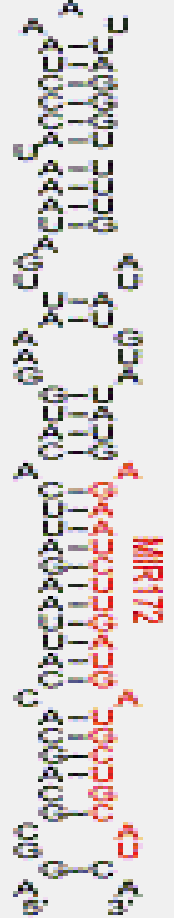
[Zhao Y, Srivastava D, TIBS 32:189,2007](#)

- Intronic miRNAs often in antisense direction, made from own promoter
- Exonic miRNAs - non-coding (or in alternatively spliced exons)

Precursor miRNA Products Form Stem Loop Structures

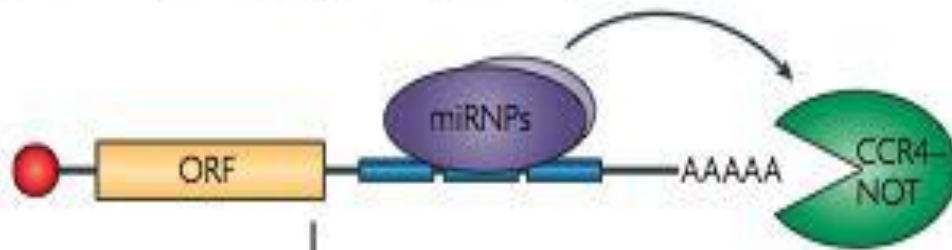


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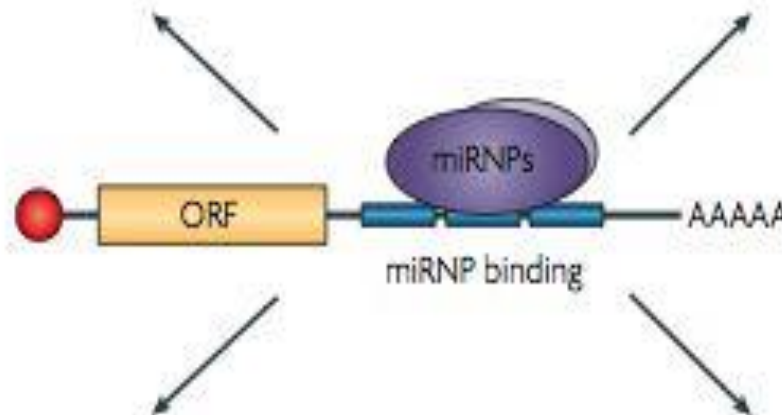
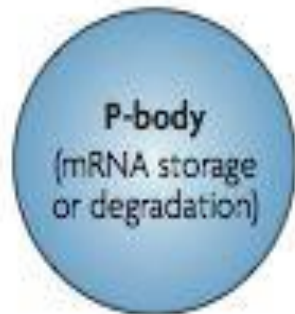
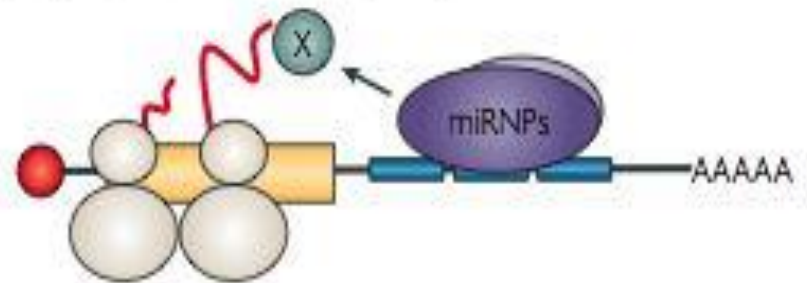
Deadenylation

(followed by decapping and degradation)



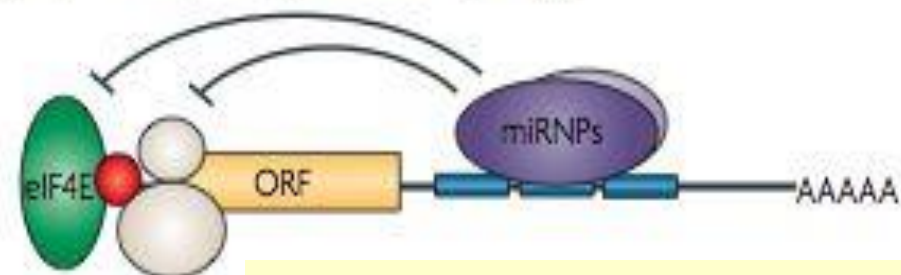
Proteolysis

(degradation of nascent peptide)



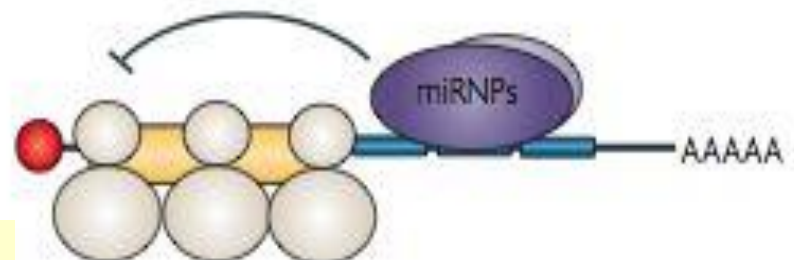
Initiation block

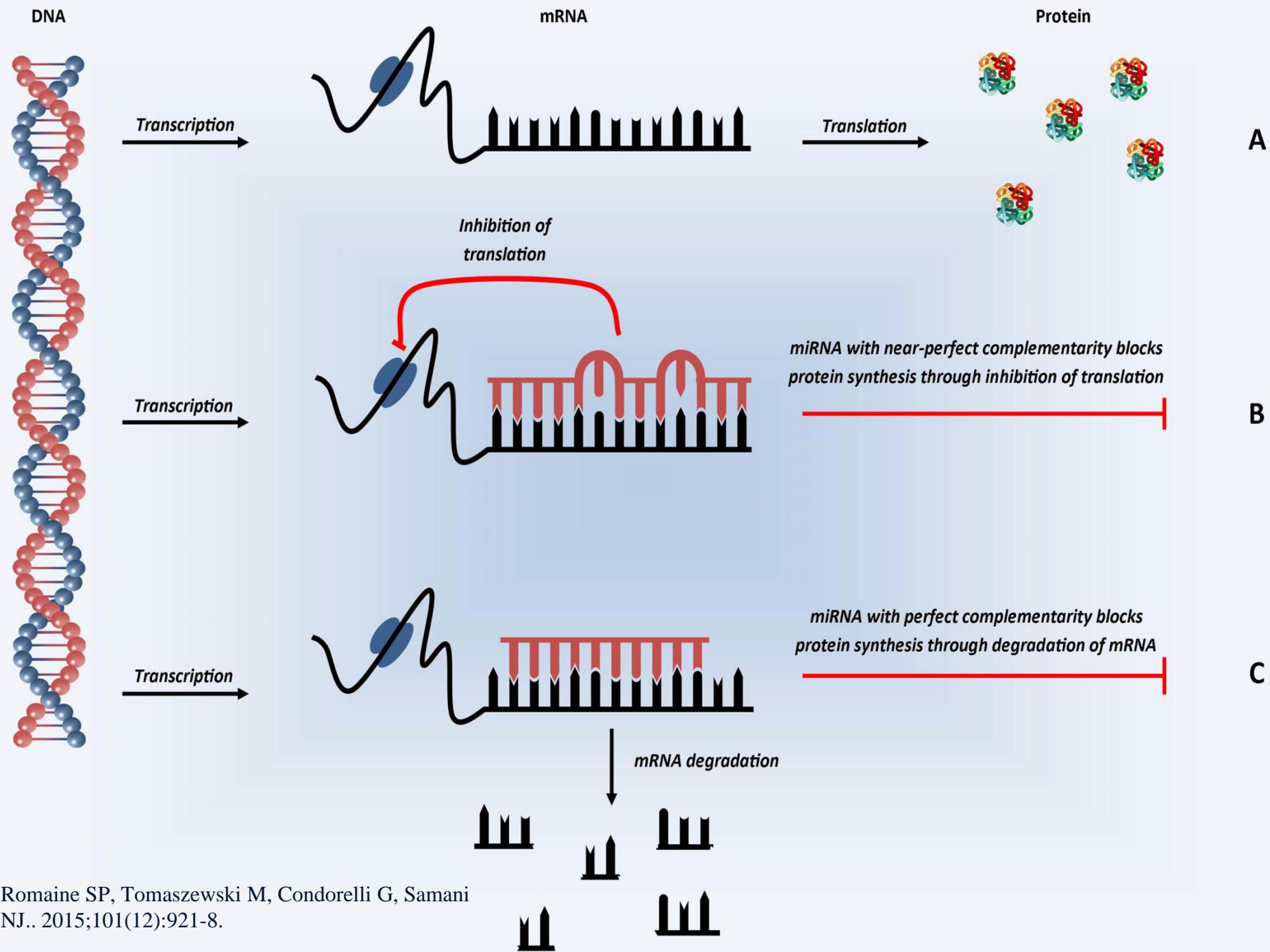
(repressed cap recognition or 60S joining)



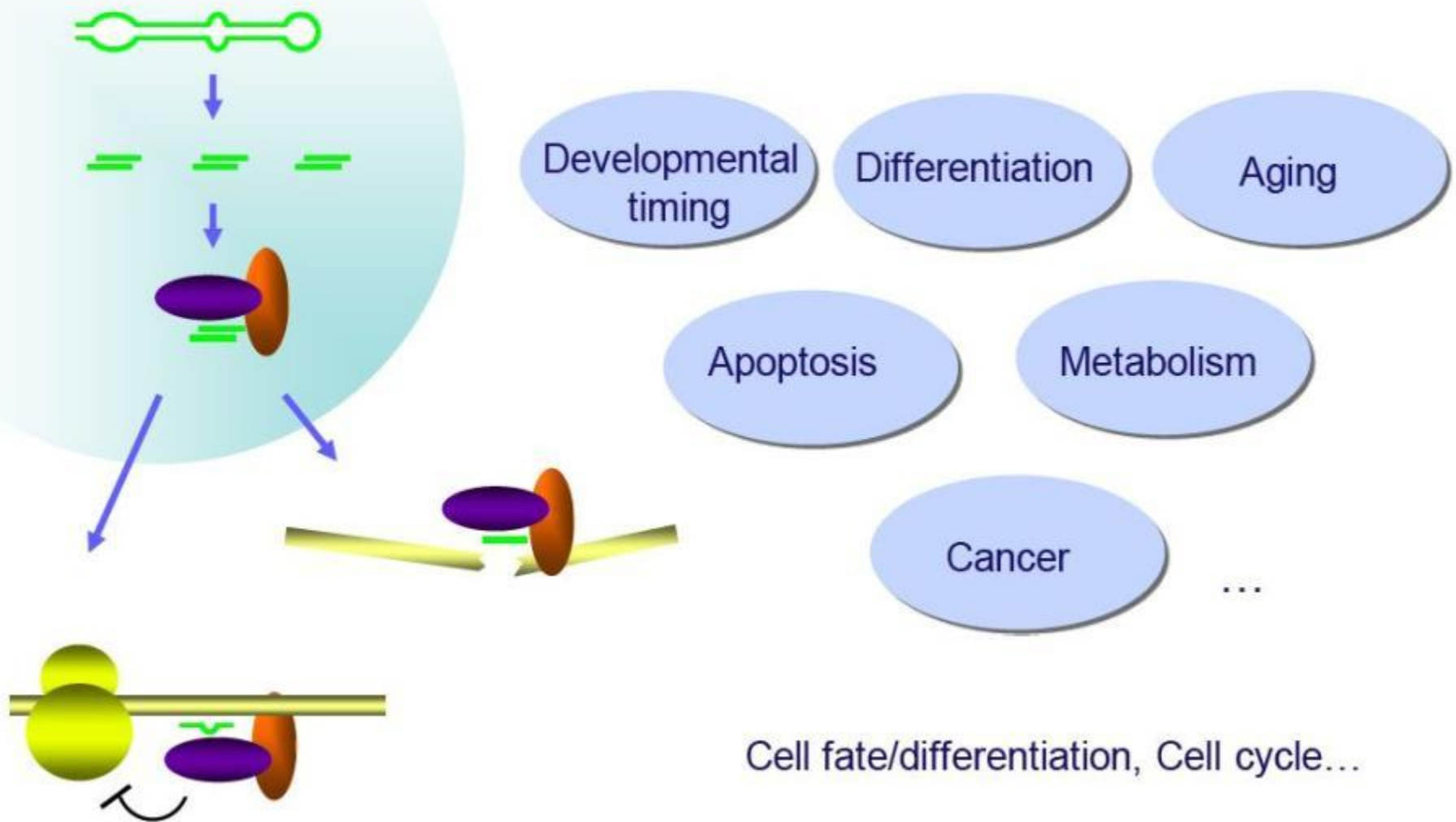
Elongation block

(slowed elongation or ribosome 'drop-off')





Thousands of microRNAs act in multiple biological events



Methods of identifying miRs

- ✓ Direct cloning
- ✓ Computer search of the genome
- ✓ MiRNA microarray search in different species
- ✓ Construction of miRNA in vitro and targeting known gene sequences

Using bioinformatics tools to identify miRs

- KEGG: [http:// www.genome.jp/kegg](http://www.genome.jp/kegg)
- Target Scan : <http://www.targetscan.org>
- miRBase: <http://www.mirbase.org>
- miRWalk: <http://www.umm.uni-heidelberg.de>
- miRanda :<http://www.microrna.org>
- miRDB : [http:// :mirdb.org](http://:mirdb.org)
- GEO: www.ncbi.nlm.nih.gov/gds
- miRNAMap: <http://mirnamap.mbc.nctu.edu.tw>



Gestational Diabetes Mellitus Overview

- ❖ Recognize for the first time during pregnancy
- ❖ Intolerance to carbohydrates with different intensities.
- ❖ The most common medical complication of pregnancy.
- ❖ Affects 2 to 9 percent of all pregnancies.
- ❖ The prevalence of GDM varies from 1-20%, and is rising worldwide
- ❖ At risk for type 2 diabetes



Pathophysiology

- ❖ Pregnancy is associated with insulin resistance (IR) and hyperinsulinemia that may predispose some women to develop diabetes.
- ❖ Hormones and adipokines secreted from the placenta, including tumor necrosis factor, human placental lactogen, and human placental growth hormone are possible causes of IR in pregnancy.
- ❖ In addition, increased estrogen, progesterone, and cortisol during pregnancy contribute to a disruption of the glucose insulin balance
- ❖ The development of GDM occurs when a woman's pancreas does not secrete enough insulin
- ❖ In addition, increased maternal adipose deposition, decreased exercise, and increased caloric intake contribute to this state of relative glucose intolerance.



insulin sensitivity during pregnancy

- ❖ In early pregnancy, insulin secretion increases, while insulin sensitivity is unchanged, decreased, or may even increase.
- ❖ At mid pregnancy, insulin sensitivity starts to decline progressively, and became worse during the rest of the pregnancy, being worst in the late third trimester.



Risk factors for GDM

- ✓ Obesity
- ✓ older maternal age
- ✓ past history of GDM
- ✓ strong family history of diabetes
- ✓ member of an ethnic group with a high prevalence of T2DM
- ✓ polycystic ovary syndrome
- ✓ persistent glucosuria
- ✓ history of delivering big baby (birth weight ≥ 4000 g)
- ✓ history of recurrent abortions
- ✓ history of unexplained stillbirths
- ✓ history of essential hypertension, or pregnancy-related hypertension



GDM complications

- ✓ Fetal macrosomia
- ✓ Damage during delivery
- ✓ Polyhydramnios
- ✓ Preeclampsia
- ✓ Newborn metabolic disorders
- ✓ Respiratory distress syndrome



Screening and diagnosis of GDM

- ✓ 24-28 weeks of pregnancy in one hour 50 g glucose challenge test (GCT)
- ✓ plasma glucose levels ≥ 140 mg / dL
- ✓ oral glucose tolerance test (OGTT)
- ✓ Carpenter and Coustan criteria: impairment in at least two stages of four measurement periods.



Screening and diagnosis of GDM

GDM Diagnostic Criteria for OGTT Testing

	75-g 2-hour*	100-g 3-hour†
Fasting plasma glucose (FPG)	≥92 mg/dL (5.1 mmol/L)	≥95 mg/dL (5.3 mmol/L)
1-hour post-challenge glucose	≥180 mg/dL (10.0 mmol/L)	≥180 mg/dL (10.0 mmol/L)
2-hour post-challenge glucose	≥153 mg/dL (8.5 mmol/L)	≥155 mg/dL (8.6 mmol/L)
3-hour post-challenge glucose		≥140 mg/dL (7.8 mmol/L)

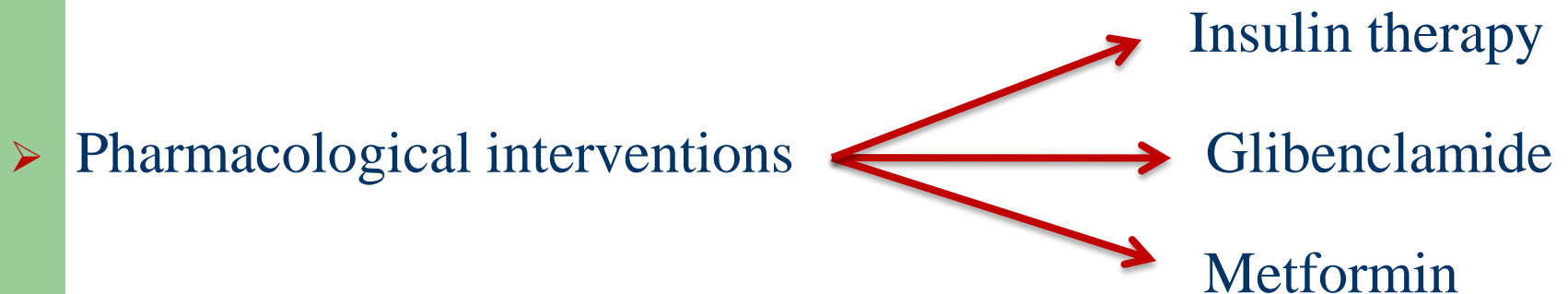
*A positive diagnosis requires that test results satisfy any one of these criteria.

†A positive diagnosis requires that ≥2 thresholds are met or exceeded.



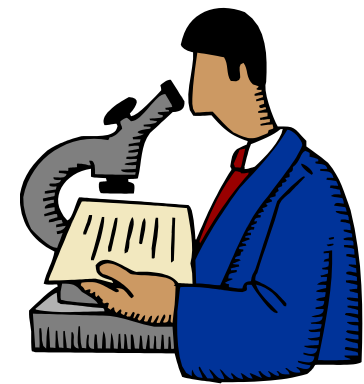
Management of GDM

- Achieve maternal near normoglycemic level
- Low-carbohydrate diet , high fibre with caloric restriction
- Frequent small snacks may be needed between meals
- Avoid starvation
- Exercise

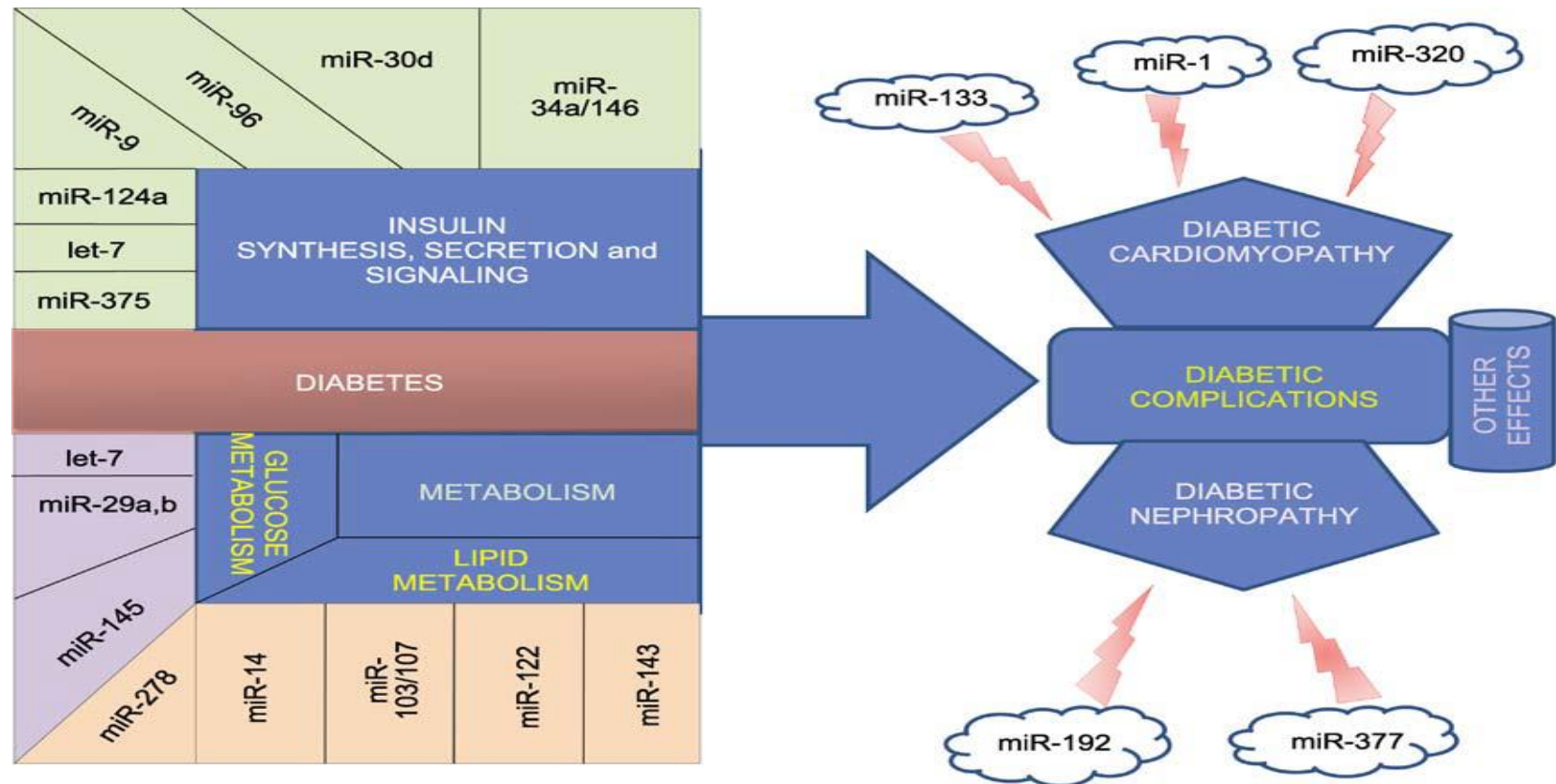


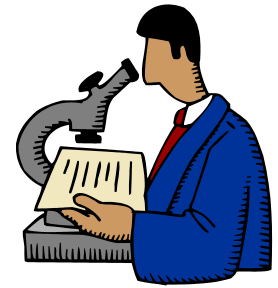
MicroRNA and Diabetes



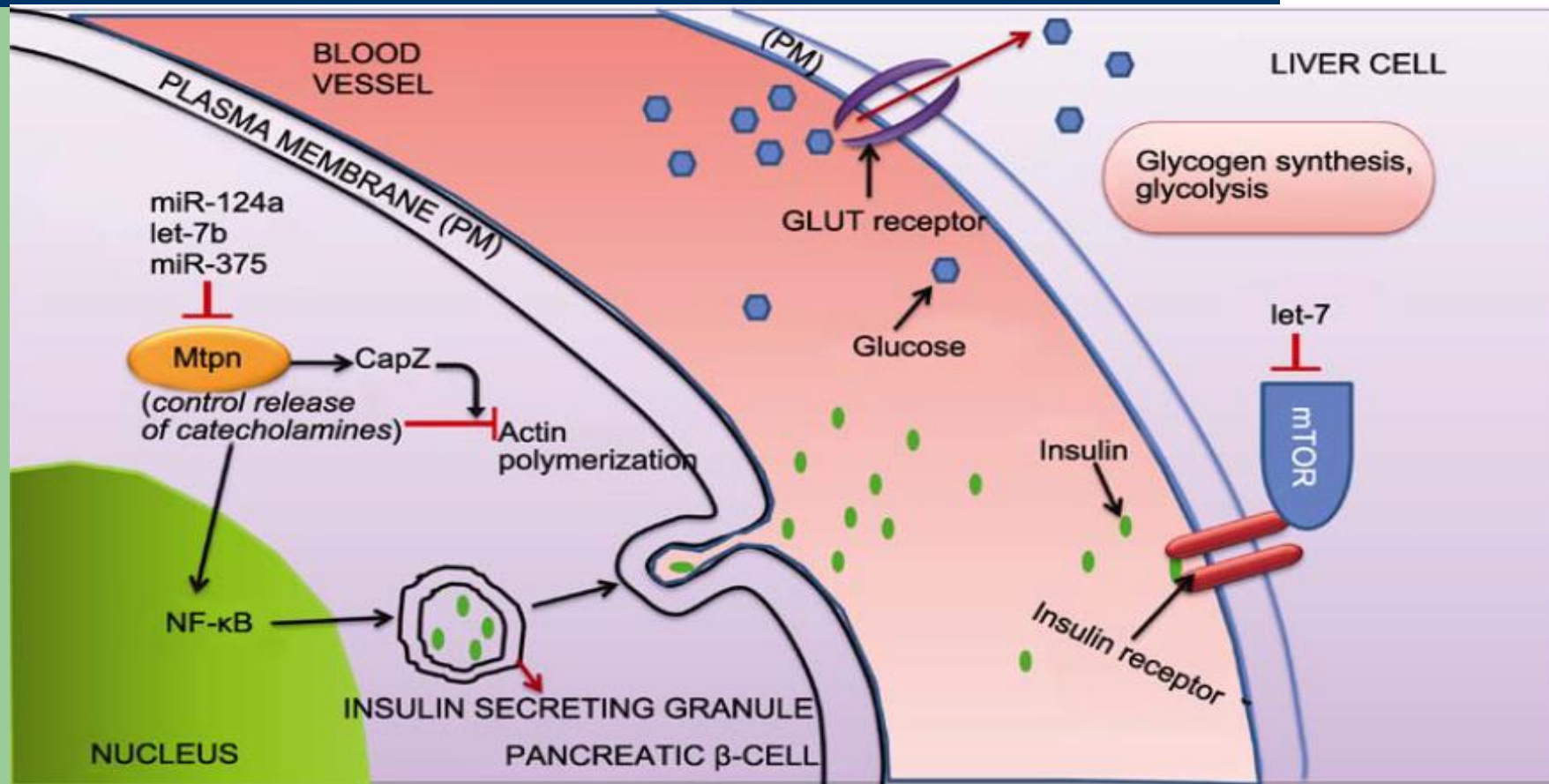


miRNAs in glucose homeostasis

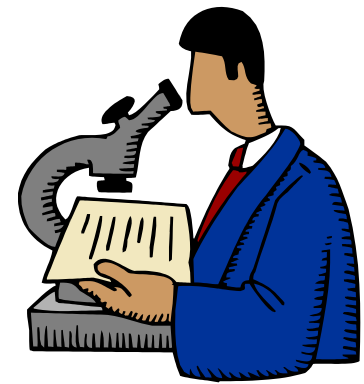




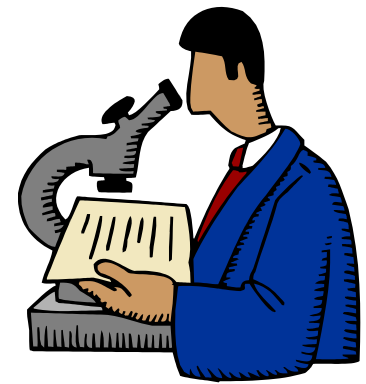
miRNAs in insulin production and secretion



miRNAs in insulin action



- ❑ **Shi et al, 2007.** of the two genes encoding insulin receptor substrate proteins(IRS1 and IRS2), only IRS1 has been identified as a target of miRNAs, specifically miR-145 .
- ❑ **Roggli et al , 2010.** implicates miR-34a and miR-146a, as well as miR-21 as novel players in β -cell failure elicited by proinflammatory cytokines during the development of peri-insulitis that precedes overt diabetes in NOD mice



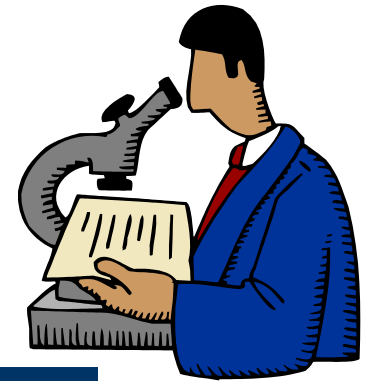
miRNAs in insulin action

- ❑ **Zhu et al , 2011.**target genes repressed by let-7 include IGF1R,INSR, IRS2, HMGA2, and IGF2BP2. These data support that let-7 is a regulator of glucose metabolism and that the let-7family is a potential target for T2D.
- ❑ **Honardoost M et al, 2014.** the role of microRNA 135a in skeletal muscle insulin resistance in mice

Target is gene INSR (Insulin receptor), which prevents its expression and thus reduce the absorption of glucose in the cell.

MiRNA135a is suppressed to reduce hyperglycemia.

MiRNAs in diabetic complications



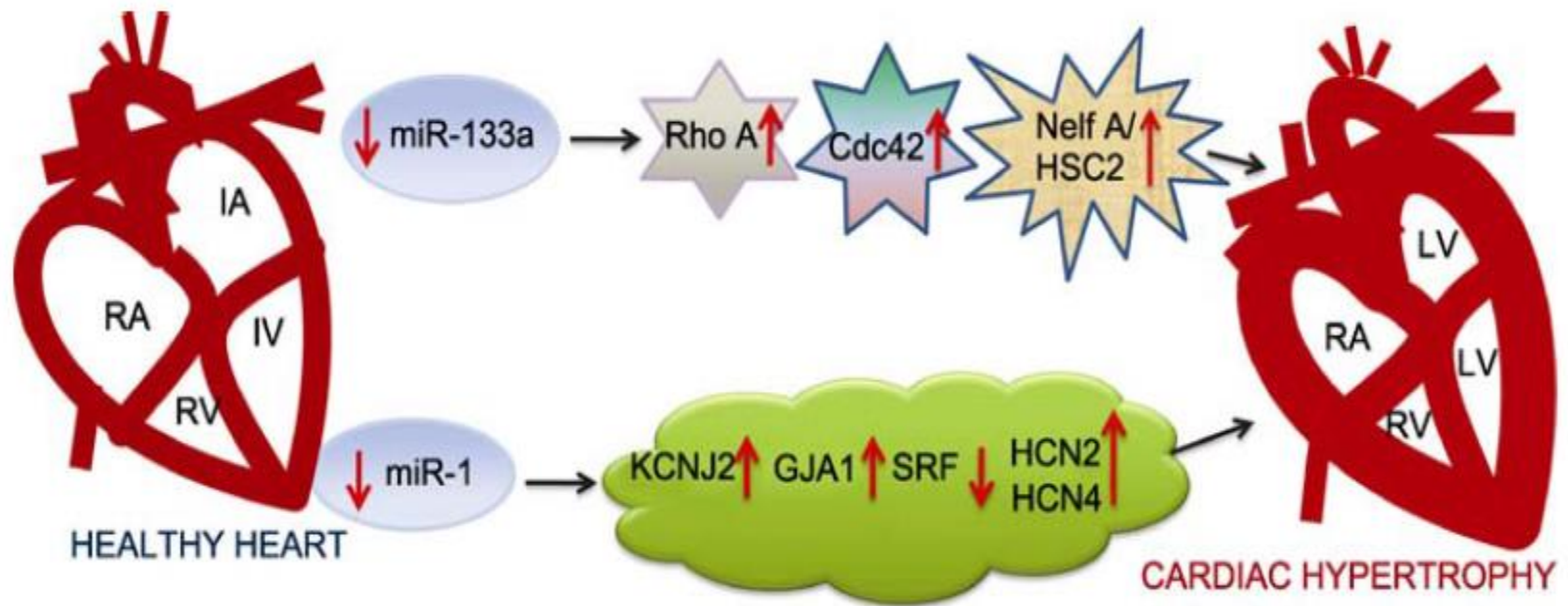
Diabetes causes complications in many organs such as:

- Diabetic cardiomyopathy
- Diabetic nephropathy
- Diabetic retinopathy
- Diabetic foot disorders

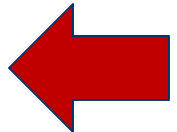
miRNAs are involved in many of these complications.

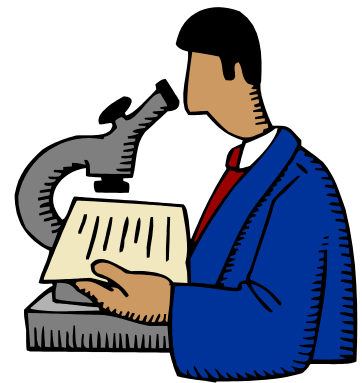


Diabetic cardiomyopathy

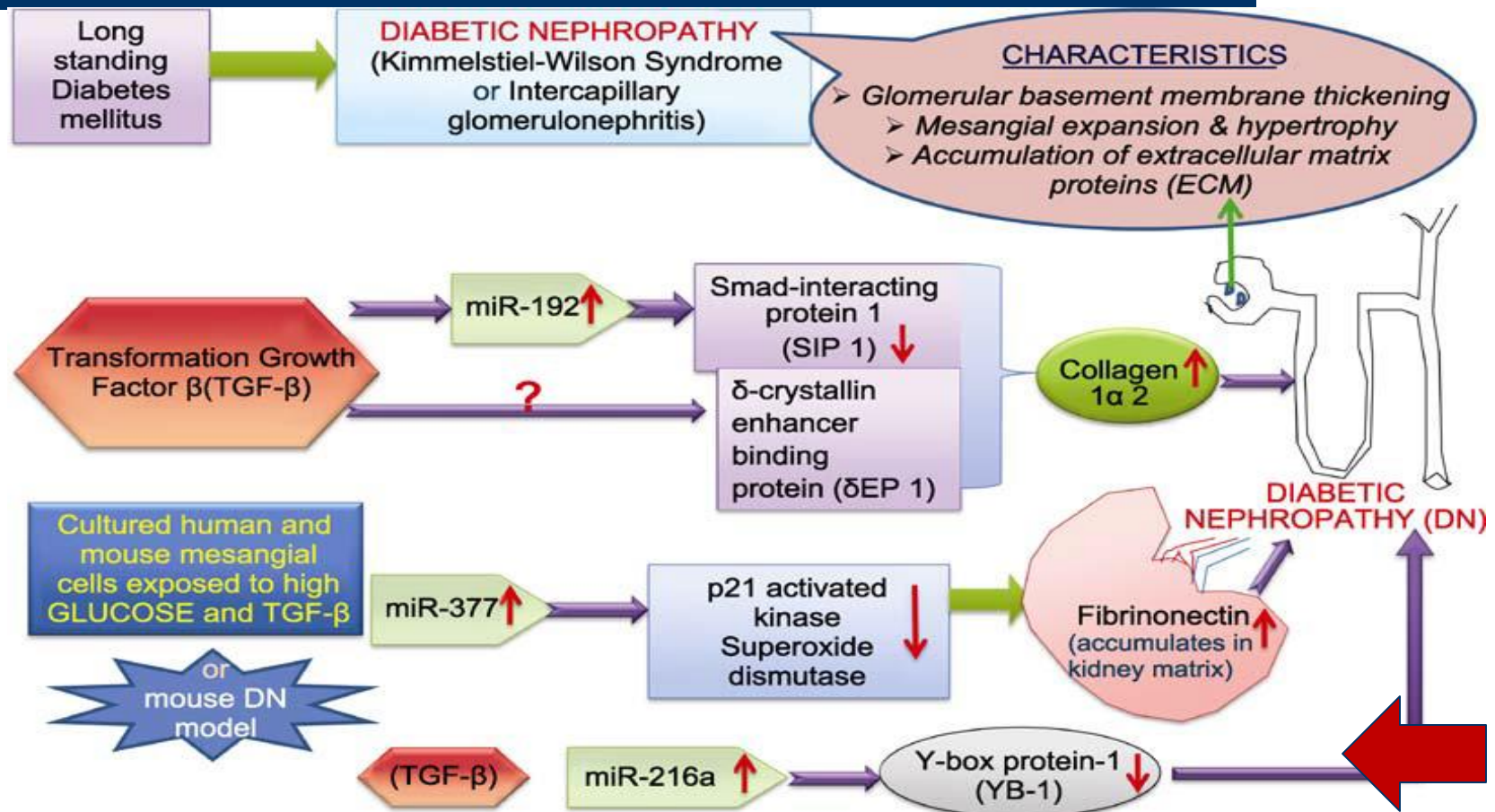


Kumar M, Nath S, Prasad HK, Sharma G, Li Y. Protein & cell. 2012;3(10):726-38.

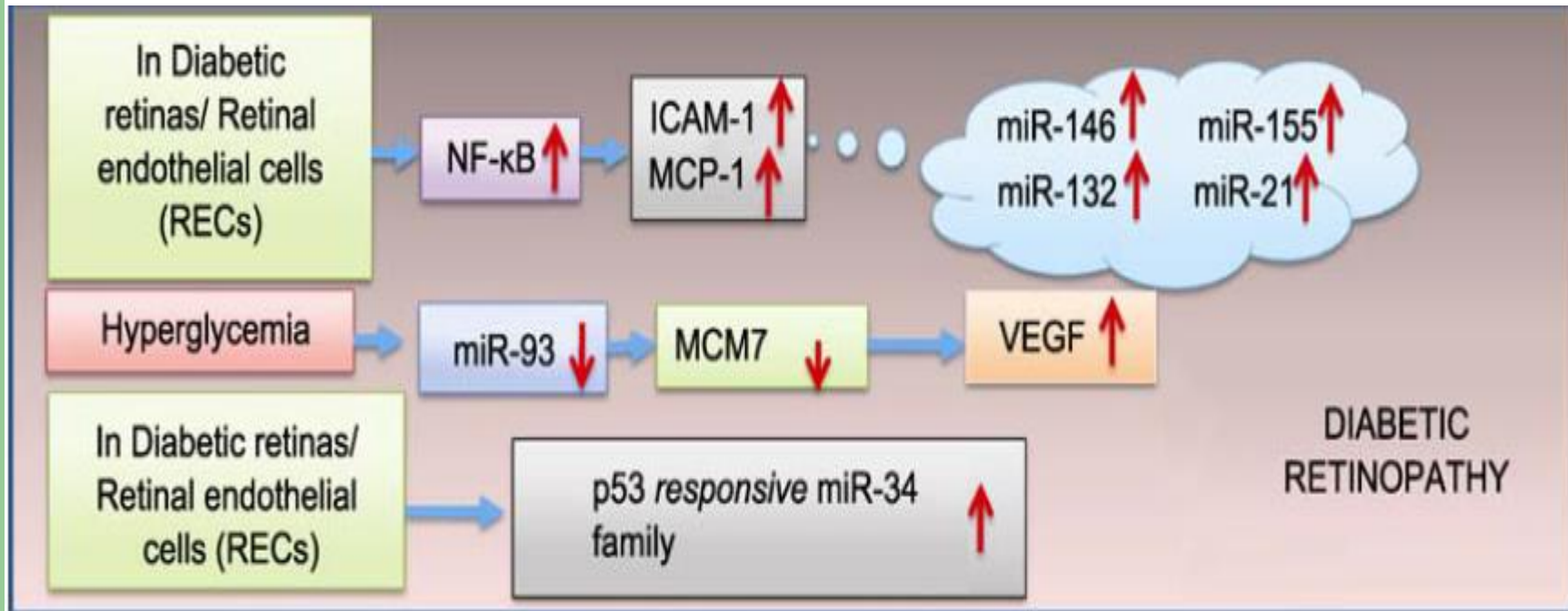
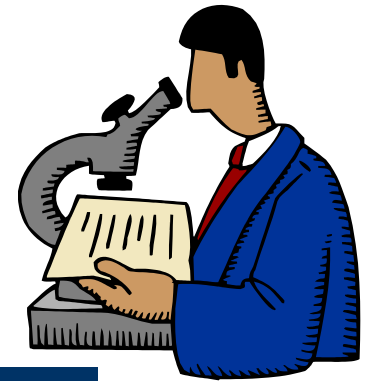




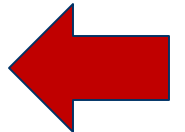
Diabetic nephropathy



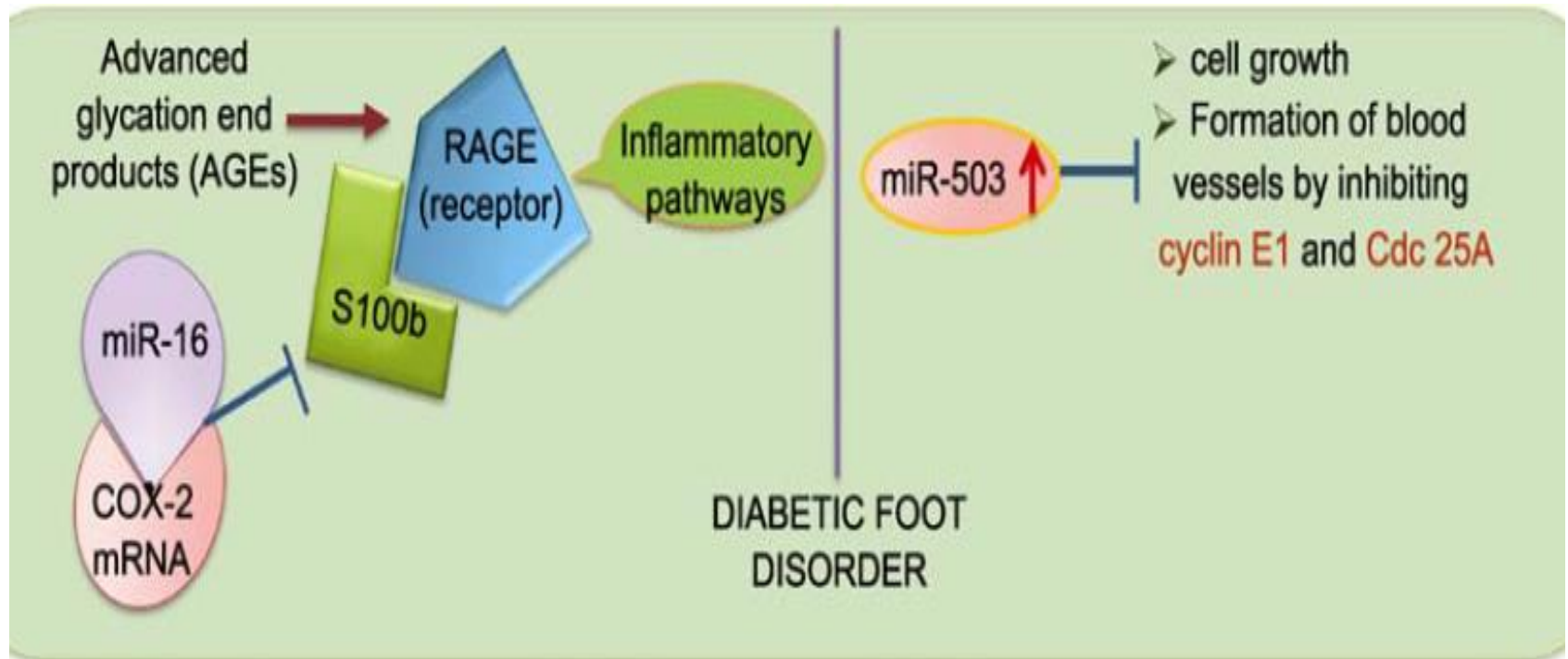
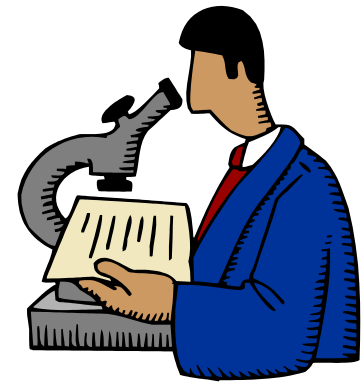
Diabetic retinopathy



Kumar M, Nath S, Prasad HK, Sharma G, Li Y. Protein & cell. 2012;3(10):726-38.

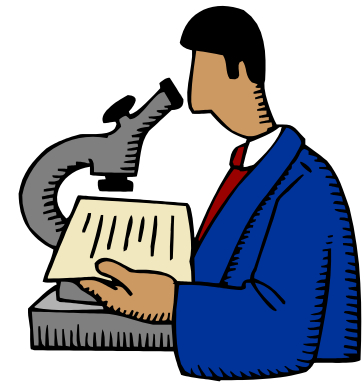


Diabetic foot disorders



Kumar M, Nath S, Prasad HK, Sharma G, Li Y. Protein & cell. 2012;3(10):726-38.

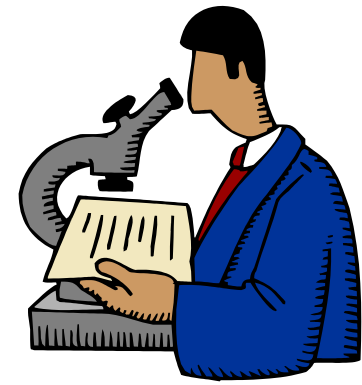
microRNAs as biomarkers in plasma or serum



2011  Diana M et al

- ❑ with Title microRNAs in pregnancy
- ❑ The study of 44 related articles
- ❑ miRNAs present in the maternal circulation may provide a new promising diagnostic tool for pregnancy disorders.


microRNAs as biomarkers in plasma or serum



2015  Tsochandaridis M et al

- ❑ with Title Circulating MicroRNAs as Clinical Biomarkers in the Predictions of Pregnancy Complications
- ❑ The study of 60 related articles
- ❑ microRNAs circulating in the maternal plasma might have the potential to be noninvasive diagnostic and prognostic biomarkers for pregnancy monitoring.
- ❑ They might prevent the development of gestational disorders and form the basis of personalized therapeutic strategies.

Microrna and Macrosomia

2015  Li J et al

- ❑ investigated the role of miR-17-92 cluster in macrosomia
- ❑ miR-17-92 cluster contribute to macrosomia development by targeting regulators of cell cycle pathway. Our findings not only provide a novel
- ❑ insight into the molecular mechanisms of macrosomia, but also the clinical value of miR-17-92 cluster
- ❑ as a predictive biomarker for macrosomia.

Microrna and Macrosomia

2014  Hua Jiang et al

- ❑ The expression levels of miR-21 were significantly decreased in macrosomia as
- ❑ compared to the controls in the third trimester. Receiver operating characteristic (ROC) curve analyses showed that the area
- ❑ under the ROC curve for miR-21 was 67.7% (sensitivity ¼ 66.7% and specificity ¼ 70.0%). Conclusions: miR-21 in maternal
- ❑ serum is differentially expressed between macrosomia and controls, and miR-21 could be used as a candidate biomarker to predict macrosomia.

miRNA and GDM

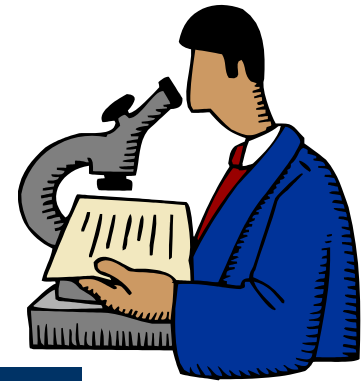


2014  Nir Pillar et al

Selection of validated targets of potential miRNA biomarkers in GDM.]

MicroRNA	miRNA expression in GDM	Target
miR-222	Down	SNX4 CDKN1B MMP1
miR-29a	Down	INSIG1 ATAD2B IGF1
miR-181a	Down	IL1A PRTG
miR-132	Down	FOXO3a
miR-1268	Up	SLC8A2 STXBP1

miRNA and GDM



2010 -2014



Yanan Zhu et al

- ❑ peripheral blood samples were collected from women at 16–19 weeks of pregnancy.
- ❑ Pooled samples from 10 women who were subsequently diagnosed with GDM and from 10 healthy controls
- ❑ Differential expression of five upregulated miRNAs (hsa-miR-16-5p, hsa-miR-17-5p, hsa-miR-19a-3p, hsa-miR-19b-3p, hsa-miR-20a-5p)
- ❑ The five miRNAs were differentially expressed in GDM could serve as noninvasive biomarkers.
- ❑ thereby contributing to the diagnosis and treatment of this disease.

miRNA and GDM




2012  Morales-Prieto et al

- ❑ Study of gene expression of microRNAs involved in the pregnancy disorder that is on chromosome number 19 and 14
- ❑ Expression of these microRNAs direct connection with pregnancy disorders

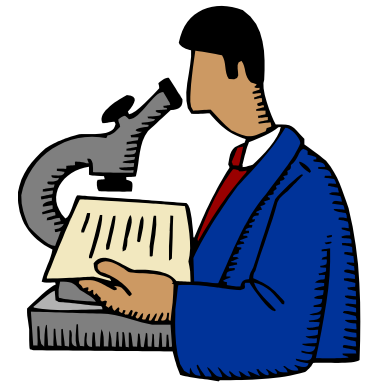
miRNA and GDM



2011  Zhao et al

- ❑ a total of 24 women with gestational diabetes and 24 nondiabetic subjects
- ❑ serum collected at 16-19 gestational weeks.
- ❑ the expression levels of three miRNAs (miR-132, miR-29a and miR-222) were significantly decreased in GDM women
- ❑ prevent the expression of microRNAs leads to increased insulin induced gene expression
- ❑ serum miRNAs are differentially expressed between GDM women and controls and could be candidate biomarkers for predicting GDM

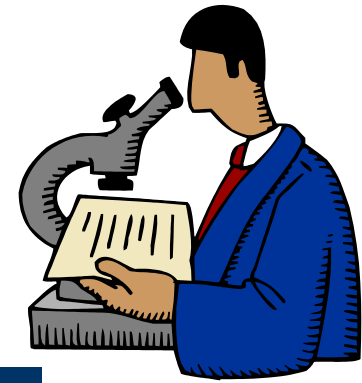
miRNA and GDM




2015  Nir Pillar et al

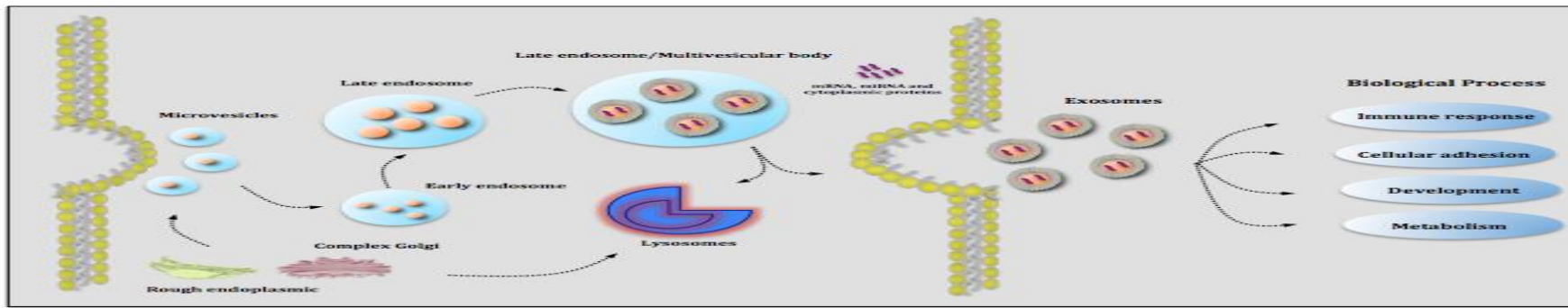
- ☐ the role of microRNAs as major factors in the pathogenesis
- ☐ as an early biomarker for the diagnosis of gestational diabetes
- ☐ prevent the development of gestational diabetes

Exosomes and GDM



2008  Taylor et al

- ❑ miRNA-203 has been identified in exosomes isolated from women with GDM.
- ❑ oxidative stress and hyperglycaemia increase the release of exosomes from the placenta into the maternal circulation during in the first trimester of pregnancy
- ❑ The characterised of exosomes in the blood of these pre-symptomatic women, thus, may be of utility as an early biomarker of disease onset.



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